UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/720,987	11/24/2003	Didier Trono	CLFR:023US	3372

7590 03/08/2007

Gina N. Shishima
Fulbright & Jaworski L.L.P.
Suite 2400
600 Congress Avenue
Austin, TX 78701

EXAMINER	
VIVLEMORE, TRACY ANN	
ART UNIT	PAPER NUMBER
1635	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
2 MONTHS	03/08/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/720,987
Filing Date: November 24, 2003
Appellant(s): TRONO ET AL.

David L. Parker
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed November 20, 2006 appealing from the Office action mailed May 25, 2006.

Information Disclosure Statement

According to 37 CFR 1.97 (d), an information disclosure statement shall be considered by the Office if filed by the applicant after the mailing date of a final action or an action that otherwise closes prosecution in the application provided that the information disclosure statement is accompanied by: (1) The statement specified in paragraph (e) of this rule; and (2) The fee set forth in § 1.17(p).

The information disclosure statement filed November 20, 2006 was accompanied by the fee set forth in § 1.17(p) but fails to comply with 37 CFR 1.97(d) because it lacks a statement as specified in 37 CFR 1.97(e). Also, nothing has been made of record to describe the relevance of the cited references to the issues under appeal. It has been placed in the application file, but the information referred to therein has not been considered.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is substantially correct. The changes are as follows:

WITHDRAWN REJECTIONS

The following grounds of rejection are not presented for review on appeal because they have been withdrawn by the examiner. The 35 USC 112, first paragraph rejections for new matter and written description and the rejection under 35 USC 103 over Yao et al., Verma et al., Elbashir et al., Elbashir et al. and Deuschle et al.

which claims ?

APPARENT TYPOGRAPHICAL ERROR IN APPELLANTS' BRIEF

In sections VI and VII of the brief, appellants refer to a rejection of claims 1-7, 9-11, 13, 41 and 46-47 as unpatentable under 35 U.S.C. § 103 over Giordano et al. ("Giordano"; Exhibit 6), ElbasherB (sic) and Deuschle and Verma. This rejection is actually over Giordano et al., Elbashir et al. (EMBO Journal), Elbashir et al. (Nature), Deuschle and Verma. Because at page 16 appellants incorporate previous arguments

regarding both Elbashir references, the omission of the second Elbashir reference from the statement of grounds of rejection to be reviewed on appeal has been assumed to be a typographical error.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

EP1229134 Giordano et al. 08-2002, cited on IDS of 11/2004 and appended to appeal brief as exhibit 6.

Elbashir et al., EMBO Journal 2001, vol. 20, pages 6877-6888, referred to by appellant as ElbasherA, cited by the examiner in the office action of 12/2005 and appended to appeal brief as exhibit 3.

Elbashir et al., Nature 2001, vol. 411, pages 494-498, referred to by appellant as ElbasherB, cited by the examiner in the office action mailed 12/2005 and appended to appeal brief as exhibit 4.

Deuschle et al. Mol. Cell. Biol. 1995, vol. 15, pages 1907-1914, cited on IDS of 2/2004 and appended to appeal brief as exhibit 5.

US 6,013,516, Verma et al. 01-2000, cited on IDS of 2/2004.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim 41, 46 and 47 stand rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claim 41 is directed a mammalian cell comprising a polynucleotide construct encoding a siRNA. Claims 46 and 47 limit claim 41 by reciting the mammalian cell is an undifferentiated cell or is an oocyte or fertilized oocyte. Because the claims are not recited as isolated, the scope of the claims would be reasonably interpreted as reading on a human including a transgenic human and is thus directed to non-statutory subject matter. It is noted that this rejection could be overcome by amendment to recite an isolated mammalian cell.

Claims 1-7, 9-11, 13, 41 and 46-47 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Giordano et al. (EP 1 229 134 A2), Elbashir et al. 2001 (EMBO Journal), Elbashir et al. 2001 (Nature), Deuschle et al. (Mol. Cell. Biol. 1995) and Verma et al. (US Patent 6,013,516).

Claims 1-7, 9-11, 13, 41 and 46-47 are drawn to a polynucleotide construct comprising a region encoding a siRNA operably linked to an externally controllable RNA polymerase III promoter (claim 1) that is a vector (claim 2) that is a lentiviral vector (claim 3) wherein the promoter is repressible by means of an externally applied agent that is an externally applied drug (claims 4-5) wherein the repressible promoter is regulated by a Tet repressor and comprises at least one *tetO* sequence (claims 6-7) and is from the TeT^R gene (claim 9) wherein the promoter is an inducible promoter by means of an externally applied agent that is tetracycline or tetracycline analogue (claims 10-11) wherein the inducible promoter is inducible as listed in claim 13. The claims are

further directed to a mammalian cell comprising the polynucleotide construct of claim 1 (claim 41) wherein the cell is an undifferentiated cell (claim 46) or an oocyte or fertilized oocyte (claim 47).

Giordano et al. teach the use of inducible and repressible transcription systems that can be used to control the timing of the expression of dsRNA from polynucleotide constructs that can be retroviral vectors which express siRNAs wherein the inducible and repressible transcription system can be the Tet promoter and the promoter can be a RNA polymerase III promoter (see sections: [0110-111], [0010-0012], [0049-0050] and [0073]). The teachings of Giordano et al. of the Tet promoter inducible and repressible transcription system is reasonably considered an inherent disclosure of a repressible promoter regulated by the Tet repressor which comprises at least one *tet*O sequence (or it would not be repressible) that is antibiotic inducible by doxycycline, a tetracycline analog. Giordano et al. teach the polynucleotide constructs of their invention as comprised in mammalian cells, stem cells and gametes (which is reasonably considered an inherent disclosure of both sperm and oocytes) (see section [0016]). Giordano et al. do not teach the use of an inducible or repressible promoter that includes both a DNA binding domain and a repressor domain.

Elbashir et al. (EMBO Journal) teach a systematic analysis of the length, secondary structure, sugar backbone and sequence specificity of siRNA duplexes used for RNAi in Drosophila and the structure of the most potent siRNA duplexes that are 21 nt long comprising a 19 nt base paired sequence with 2 nt 3' overhanging ends (see "siRNA users guide": pg. 6885). Elbashir et al. teach that siRNAs are valuable reagents

for inactivation of gene expression, not only in insect cells but also in mammalian cells, with great potential for therapeutic application (pg. 6884, col. 2).

Elbashir et al. (Nature) teach that the mediators of sequence specific messenger RNA degradation in mammalian cells are 21 and 22 nucleotide small interfering RNAs, that 21 nucleotide siRNA duplexes specifically express expression of endogenous and heterologous genes in different mammalian cell lines and that therefore 21 nt siRNAs provide a new tool for studying gene function (Abstract). Elbashir et al. teach that siRNAs are extraordinarily powerful reagents for mediating gene silencing and that siRNAs are effective at concentrations that are several orders of magnitude below the concentrations applied in conventional antisense or ribozyme gene targeting experiments (pg. 496, col. 2).

Deuschle et al. teach tetracycline reversible promoters that are controlled by a tetracycline controlled transrepressor protein that is a tetR-KRAB fusion protein that is reasonably considered to be a polypeptide regulator that comprises a DNA binding domain and a repressor domain (pg. 1907, col. 1-2). Deuschle et al. teach the tetR-KRAB silencing system as useful as a genetic switch for regulating the expression of heterologous and endogenous genes, that their data offers a novel way to regulate gene expression in higher mammalian cells and that the tetR-KRAB fusion protein offers the unique possibility of reversibly down regulating the expression of cellular genes on top of their normal cellular regulation (Abstract, pg. 1913, col. 2).

Verma et al. teach lentiviral vectors that express heterologous nucleic acid sequences that are operably linked to a regulatory nucleic acid sequence that can be a promoter and that a wide range of promoters, including suitable viral and mammalian

promoters are known in the art (col. 6, lines 24-29). Verma et al. teach that the lentiviral vectors of their invention can be used to express antisense nucleic acids and ribozymes to inhibit gene expression in mammalian cells (col. 7).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the instant invention was made to formulate a polynucleotide construct comprising a region encoding a siRNA (as taught by Elbashir et al.) operably linked to an externally controllable promoter that was a lentiviral vector construct wherein expression of the siRNA was regulated by a TetR-KRAB operator/repressor system (as taught by Giordano et al., Verma et al. and Deuschle et al.) wherein the externally controllable promoter was repressible by means of an externally applied agent that is an externally applied drug, wherein the repressible promoter was regulated by a Tet repressor and comprises at least one *tet*O sequence and is from the TeT^R gene wherein the promoter is an inducible promoter by means of an externally applied agent that is tetracycline or tetracycline analogue, in order to transduce mammalian cells, including stem cells (as taught by Giordano et al.) for the purposes of studying gene function, particularly in differentiating stem cells, by down regulating the expression of cellular genes on top of their normal regulation (as taught by Giordano et al., Elbashir et al. and Deuschle et al.).

One of ordinary skill in the art would have been motivated to construct the above polynucleotide construct in order to down regulate the expression of cellular genes on top of their normal regulation, thereby providing a specific means of studying gene function in a mammalian cell by controlling the expression of an siRNA (as taught by Giordano et al., Elbashir et al., Verma et al. and Deuschle et al.) and because Deuschle et al. teach the utility of the tetR-KRAB silencing system as a genetic switch for

regulating the expression of heterologous and endogenous genes, that this system offers a novel way to regulate gene expression in higher mammalian cells and that the tetR-KRAB fusion protein offers the unique possibility of reversibly down regulating the expression of cellular genes on top of their normal cellular regulation.

One of ordinary skill in the art would have expected success in constructing the above polynucleotide construct because all of the individual elements required by the claimed construct are were known and used successfully in the prior art of regulating the expression of cellular genes in mammalian cells, because the functional anatomy of siRNAs that are effective in mammalian cells was known, because the siRNAs described by Elbashir et al. provide a new tool for studying gene function, because siRNAs are extraordinarily powerful reagents for mediating gene silencing and are effective at concentrations that are several orders of magnitude below the concentrations applied in conventional antisense or ribozyme gene targeting experiments (as taught by Elbashir et al.), because Giordano et al. teach the successful construction of the above polynucleotide construct in a retroviral vector, because lentiviral vectors are retroviral vectors that are taught by Verma et al. as viral vectors that will express heterologous nucleic acid sequences that are operably linked to a regulatory nucleic acid sequence that can be any of a wide range of promoters, including suitable viral and mammalian promoters that are known in the art, and Verma et al. teach that lentiviral vectors can be used to express antisense nucleic acids and ribozymes to inhibit gene expression in mammalian cells. Therefore, one of skill would have expected success in formulating a retroviral vector for inducible or repressible control of expression of siRNAs in mammalian cells using the TetR-KRAB

operator/repressor system (as taught by Deuschle et al. for example), wherein the mammalian cells were undifferentiated cells or oocytes (as taught by Giordano et al.) wherein the vector was a lentiviral vector known to be effective at delivering and expressing nucleic acids to mammalian cells (as taught by Verma et al.).

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

(10) Response to Argument

Appellants traverse the rejection of claims 41, 46 and 47 under 35 USC 101 by admitting the claims could cover some future transgenic human but assert the claims are not "directed to" a transgenic human. While it is correct that the scope of the claims is not limited to a transgenic human, humans are within the claim scope and therefore the claims are directed to non-statutory subject matter. With regard to claims 46 and 47, appellants assert these claims cannot be interpreted to read on a whole human. This argument is not persuasive with regard to claim 46 because an undifferentiated cell could be within a human and therefore this limitation does not overcome the non-statutory scope of claim 41. With regard to claim 47, appellants appear to argue a fertilized oocyte is not a "whole human", without defining what makes a human "whole". While it is not understood what would be a partial human, the prohibition under 35 USC 101 of claims directed to humans does not specify they have to be "whole".

Appellants further argue that the examiner's rejection implies that a claim directed to a transgenic DNA sequence could also be read to cover some hypothetical transgenic human, and further assert such claims are routinely issued as are claims to transgenic mammalian cells. These arguments are not persuasive because they are not directed to the claims under appeal but to possible interpretation of claims in other patents and/or applications.

Appellants traverse the rejection of claims 1-7, 9-11, 13, 41, 46 and 47 under 35 USC 103 over Giordano et al., Elbashir A, Elbashir B, Deuschle et al. and Verma et al. by arguing they have been unable to find any teaching or suggestion in Giordano of a siRNA operably linked to an externally controllable RNA polymerase III promoter, wherein expression of the siRNA is regulated by a polypeptide regulator having both a DNA binding domain and a repressor domain. Appellants acknowledge that Giordano teaches a DNA binding domain such as is found in the TetR but argue they can not find any suggestion to use a polypeptide regulator having both a DNA binding domain and a repressor domain such as TetR/KRAB.

It is correct that the Giordano reference alone does not teach all elements of the claims; otherwise the rejection would have been applied under 102. Giordano et al. teach constructs for expressing siRNAs and explicitly suggest the use of pol III promoters at column 3, lines 54-58. Giordano further teach (see example 1, columns 32-36) that the promoter can be externally controllable, for example the TetR system. The Deuschle reference is relied upon to teach a polypeptide regulator having a DNA binding domain and a repressor domain such as TetR/KRAB.

Appellants further argue the Giordano reference teaches away from using a polypeptide regulator for inhibiting RNA polymerase III, citing column 33, lines 19-21. This argument is not persuasive because the cited column and lines do not teach that polypeptide regulators do not work with a pol III promoter and therefore is not a teaching away from use of pol III promoters. In fact, pol III promoters are explicitly suggested at numerous points in the reference, including at paragraph 111.

With regard to the Verma reference, appellants argue Verma teaches lentiviruses in general and their use in expressing heterologous nucleic acids, but that Verma is silent with respect to siRNA expression constructs operably linked to an externally controllable RNA polymerase III promoter, wherein expression of the siRNA is regulated by a polypeptide regulator having both a DNA binding domain and a repressor domain. Appellants are correct that Verma does not teach expression of siRNAs; Verma is relied upon to provide teaching of what is known in the art, use of retroviral vectors such as lentiviral vectors for expression of heterologous genes. Expression of siRNAs through externally controllable RNA polymerase III promoters is taught by Giordano, polypeptide regulators having a DNA binding domain and a repressor domain are taught by Deuschle.

With regard to the Elbashir references, appellants argue these references relate generally to siRNA expression constructs but do not appear to teach or suggest their being operably linked to an externally controllable RNA polymerase III promoter, wherein expression of the siRNA is regulated by a polypeptide regulator having both a DNA binding domain and a repressor domain. Appellants are correct, the Elbashir references do not teach operable linkage of siRNAs to externally controllable RNA

polymerase III promoters having a polypeptide regulator having both a DNA binding domain and a repressor domain, these teachings are provided by the Giordano and Deuschle references.

Appellants acknowledge that the Deuschle reference teaches an externally controllable promoter having a DNA binding domain and a repressor domain (TetR-KRAB), but argue they are unable to find any teaching of use of such a promoter in the context of a siRNA under the control of a pol III promoter as specified in the claims. Appellants further argue the constructs of Deuschle use the CMV promoter, which is a pol II, not a pol III, promoter and that the only heterologous gene described in Deuschle as under the control of TetR-KRAB is the firefly luciferase gene. Appellants are correct that Deuschle does not teach all elements of the claims, a rejection under 35 USC 103 based on the teachings of a combination of references. Expression of siRNAs and the use of pol III promoters are teachings found in the Giordano reference.

Appellants argue the Examiner has failed to demonstrate that the references are properly combinable, asserting that the only references relied upon that concern siRNA, the Elbashir references, fail to teach the concept of controlled expression of siRNA and further stating their inability to identify any such teaching in any of the references relied upon for the rejection. Based on these assertions, appellants state they fail to understand the basis for combining the Elbashir references with the other references, citing the individual teachings of Deuschle of a CMV promoter regulated by TetR-KRAB, and asserting the examiner has failed to explain how this reference is combinable with references that concern other required aspects of the claims, such as siRNA expression. Appellants speculate the Examiner may be attempting to rely on the

disclosure of antisense and ribozyme expression in Verma to teach expression of siRNAs and argue antisense and ribozymes are dramatically different from siRNAs. Appellants assert the examiner has failed to enunciate any motivation to combine the references and further argue the examiner must adequately explain the motivation to combine separate teachings directed to 1) externally regulatable siRNA expression, 2) under the control of an RNA polymerase III promoter, 3) where the siRNA expression is regulated by a polypeptide regulator having both a DNA binding domain and a repressor domain (such as TetR/KRAB).

Appellants are incorrect that the Elbashir references are the only ones that concern siRNA. Giordano teaches externally controllable expression of siRNAs using inducible promoters such as tetR. The teachings of Verma are not relied upon to teach expression of siRNAs, this is found in the Giordano reference. In addition to the teachings of the Elbashir references, that siRNAs are powerful reagents for mediating gene silencing that are effective at concentrations several orders of magnitude below those applied in conventional antisense or ribozyme experiments and provide a new tool for studying gene function, Giordano et al. teach siRNA expression and explicitly suggest use of an externally controllable system such as TetR and use of RNA polymerase III promoters in example 1. Deuschle et al. teach the tetR/KRAB fusion protein, a polypeptide regulator having both a DNA binding domain and a repressor domain and provide a motivation to use this regulator in an expression construct by teaching this system is a genetic switch for regulating the expression of heterologous and endogenous genes that offers a novel way to regulate gene expression in higher

mammalian cells and also offers the unique possibility of reversibly down regulating the expression of cellular genes on top of their normal cellular regulation.

Appellants further argue the examiner must demonstrate on the record that one of ordinary skill had a reasonable expectation that such a combination would be successful. This is on the record in the rejection and reiterated here. One of ordinary skill in the art would have expected success in producing a polynucleotide construct comprising an externally controllable pol III promoter and a region encoding a siRNA wherein expression of the siRNA is regulated by a polypeptide regulator having a DNA binding domain and a repressor domain because all of the individual elements required by the claimed construct are were known and used successfully in the prior art. Giordano et al. teach the use of retroviral vectors to express siRNA under control of an externally controllable pol III promoter, Verma et al teach lentiviral vectors are a type of retroviral vector that have been successfully used to express heterologous nucleic acid sequences and Deuschle et al. teach successful use of the TetR-KRAB operator/repressor system to provide the possibility of reversibly down regulating the expression of cellular genes on top of their normal cellular regulation.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Tracy Vivlemore, Ph.D.

February 26, 2007

Conferees:

RICHARD SCHNIZER, PH.D.
PRIMARY EXAMINER

Richard Schnizer, primary examiner

James Schultz, supervisory primary examiner

Ram Shukla, supervisory primary examiner